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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,428	HEINDL ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *18-23,32,34,35 and 37-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *35,37 and 44* is/are allowed.

6)☒ Claim(s) *18-23,32,34 and 38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE filed on December 11, 2006 and the amendment filed on October 23, 2006 have been entered. The claims pending in this application are claims 18-23, 32, 34, 35, and 37-44. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on October 23, 2006.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. New Matter

Claims 18-23, 40, 41, and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Although the specification describes preparation of 3' LC Red 640 labeled oligonucleotide (see page 12, second paragraph), the specification fails to define or provide any disclosure to support a single-stranded oligonucleotide carrying a FRET acceptor entity but not carrying a FRET donor entity recited in claims 18, 20, 40, and 41. Furthermore, the FRET acceptor entity recited in claims 18, 20, 40, and 41 is read as any kind of FRET acceptor entity which represents genus of FRET acceptor entity while 3' LC Red 640 in the specification represents one of species of FRET acceptor entity.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application".

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 18 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Bao *et al.*, (US Patent No. 5,866,336, published on February 2, 1999).

Regarding claim 18, since Bao *et al.*, teach a composition for detection of a subject nucleic acid comprising a first nucleic acid probe that hybridizes to a first nucleic acid target sequence on the subject nucleic acid, forms a stem-loop structure when not bound to the first nucleic acid target sequence, and incorporates a resonance energy transfer donor moiety; and a second nucleic acid probe that hybridizes to a second nucleic acid target sequence on the subject nucleic acid, forms a stem-loop structure when not bound to the second nucleic acid target sequence, and incorporates a resonance energy transfer acceptor moiety, wherein the first nucleic acid target sequence and the second nucleic acid target sequence are separated by a number of nucleotides on the subject nucleic acid such that a resonance energy transfer signal from interaction between the donor moiety of the first nucleic acid probe and the acceptor moiety of the second nucleic acid probe can be detected to determine hybridization of both the first nucleic acid probe and the second nucleic acid probe to the subject nucleic acid, wherein the first nucleic acid probe further incorporates a quencher moiety, such that an interaction between the donor moiety of the first nucleic acid probe and the quencher moiety can be detected to differentiate between the first nucleic acid probe in the stem-loop structure and non-stem-loop structure, and wherein the second nucleic acid probe further incorporates a quencher moiety, such that an interaction between the acceptor moiety of the second nucleic acid probe and the quencher moiety can be detected to differentiate between the second nucleic acid probe in the stem-loop structure and non-stem-loop structure (claims 1-3 and 43 in columns 53 and 56 and Figures 1 and 2) and claim 18 does not require that the first single-stranded oligonucleotide and the second single-stranded oligonucleotide are complete single stranded oligonucleotides before hybridization, Bao *et al.*, disclose that a solution comprising a plurality of fluorescence

resonance energy transfer (FRET) hybridization probes comprising first oligonucleotide (ie., the partial single stranded first nucleic acid probe) carrying a FRET donor entity (ie., FAM, see claim 7 in column 54) and at least one second entity (ie., the quencher), said second entity being a compound (ie., DABCYL in Figure 2) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) and a second oligonucleotide (ie., the partial single stranded second nucleic acid probe) carrying a FRET acceptor entity (ie., Cy3 in Figure 2) but not carrying a FRET donor entity wherein the FRET donor entity (ie., FAM) of the first oligonucleotide and the FRET acceptor entity (ie., Cy3) of the second oligonucleotide are a FRET pair, wherein the first and second oligonucleotides are single-stranded over their full length (ie., the first and second nucleic acid probes taught by Bao *et al.,* are single-stranded over their full length after they hybridize to the subject nucleic acid, see Figure 2) as recited in claim 18.

Regarding claim 19, since Bao *et al.,* teach that FAM connects DABCYL by G-hydrogen bond-C (see Figures 12A and 12B), Bao *et al.,* disclose that the FRET donor entity (ie., FAM) and the second entity (ie., DABCYL) are carried on adjacent nucleotides of the first oligonucleotide (ie., the partial single stranded first nucleic acid probe) as recited in claim 19.

Regarding claim 22, since Bao *et al.,* teach a complex formed by a subject nucleic acid, a first nucleic acid probe and a second nucleic acid probe (see claim 1 in column 53 and claim 43 in column 56), Bao *et al.,* disclose further comprising a nucleic acid sample (ie., the subject nucleic acid).

Regarding claim 43, Bao *et al.,* teach a kit comprising the solution of claim 18 (see column 8, second paragraph).

Therefore, Bao *et al.*, teach all limitations recited in claims 18, 19, 22, and 43.

Response to Arguments

In page 8, first and second paragraphs of applicant's remarks, applicant argues that "[C]laim 18 has been amended solely in the interest of furthering prosecution and not out of acquiescence to or agreement with the Examiner. Amended claim 18 sets forth that the first and second oligonucleotides are single-stranded over their full length. In contrast, Bao discloses oligonucleotides that form a stem-loop structure. The Examiner appears to agree that Bao does not disclose or suggest first and second oligonucleotides that are single-stranded over their full length. See, page 4 of the present Official Action. Because Bao does not disclose or suggest each and every element of the claimed invention, the Examiner is respectfully requested to withdraw this rejection".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since claim 18 does not require that the first single-stranded oligonucleotide and the second single-stranded oligonucleotide are complete single stranded oligonucleotides before hybridization and Bao *et al.*, teach that the first and second nucleic acid probes are single-stranded over their full length after they hybridize to the subject nucleic acid (see Figure 2), Bao *et al.*, do disclose that the first and second oligonucleotides are single-stranded over their full length as recited in claim 18.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bao *et al.*, as applied to claims 19, 20, 22, and 43 above, and further in view of Nazarenko *et al.*, (US Patent No. 5,866,336, published on February 2, 1999).

The teachings of Bao *et al.*, have been summarized previously, *supra.*

Bao *et al.*, do not disclose further comprising at least one other component selected from a group consisting of a nucleic acid amplification primer, a template dependent nucleic acid polymerase, at least one deoxynucleoside triphosphate and a buffer for template dependent nucleic acid amplification reaction as recited in claim 23. However, Bao *et al.*, indicate that their nucleic acid probes are used in amplification reactions as primers (see column 15, first paragraph).

Nazarenko *et al.*, teach an upstream hairpin primer and a reverse primer (see Figure 2).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art

at the time the invention was made to have made a solution recited in claim 23 by adding a nucleic acid amplification primer so that the nucleic acid amplification primer and one of nucleic acid probes taught by Bao *et al.,* form a primer pair in view of patents of Bao *et al.,* and Nazarenko *et al.*. One having ordinary skill in the art has been motivated to do so because Bao *et al.,* indicate that their nucleic acid probes are used in amplification reactions as primers (see column 15, first paragraph). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to add a nucleic acid amplification primer so that the nucleic acid amplification primer and one of nucleic acid probes taught by Bao *et al.,* form a primer pair.

Response to Arguments

In page 8, fourth to sixth paragraphs of applicant's remarks, applicant argues that "[B]ao does not disclose or suggest a solution comprising first and second oligonucleotides that are single-stranded over their full length. Nazarenko does not supply the missing elements of Bao with respect to claims 18 and 23. Further, Bao and Nazarenko do not disclose or suggest a solution comprising first, second and third oligonucleotides wherein the first and third oligonucleotides are each labeled with one corresponding member of a FRET pair, as set forth in claims 20 and 23.

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since claim 18 does not require that the first single-stranded oligonucleotide and the second single-stranded oligonucleotide are complete single stranded oligonucleotides before hybridization and Bao *et al.,* teach that the first and second nucleic acid probes are single-stranded over their full length after they hybridize to the subject nucleic acid

(see Figure 2), Bao *et al.,* do disclose that the first and second oligonucleotides are single-stranded over their full length as recited in claim 18. Second, although Bao and Nazarenko do not disclose or suggest a solution comprising first, second and third oligonucleotides wherein the first and third oligonucleotides are each labeled with one corresponding member of a FRET pair as recited in claim 20, since claim 23 is also dependent on claim 18, the rejection is maintained.

8. Claims 32, 34, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bao *et al.,* as applied to claims 19, 20, 22, and 43 above, and further in view of Wittwer *et al.,* (US Patent No. 6,635,427, priority date: August 11, 2000).

The teachings of Bao *et al.,* have been summarized previously, *supra.*

Regarding claim 33, in view of claims 18 and 32 and above rejection under 35 U.S.C 102, Bao *et al.,* teach all limitations of claim 32 except a nitroindole moiety.

Regarding claims 34 and 38, since clams 19 and 34 are identical while claims 22 and 38 are identical, Bao *et al.,* teach claims 34 and 38.

Wittwer *et al.,* teach a single-stranded oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity (see column 43, claims 1 and 2).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a solution comprising a first single-stranded oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity in view of the patents of Bao *et al.,* and Wittwer *et al.*. One having ordinary skill in the art would have been motivated to do so because Wittwer *et al.*,

have taught a first single-stranded oligonucleotide carrying a FRET donor entity and a nitroindole moiety capable of quenching fluorescence of said FRET donor entity and the simple substitution of one kind of fluorescent quencher (ie., Dabayl taught by Bao *et al.,*) from another kind of fluorescent quencher (ie., a nitroindole moiety taught by Wittwer *et al.,*) during the process of making a solution recited in claim 32, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

I. In page 10, first to third paragraphs of page 10, applicant argues that "[T]he combined disclosures of Bao and Wittwer do not disclose or suggest first and second oligonucleotides that are single-stranded over their full length and comprise a FRET pair. Bao discloses dual nucleic acid probes that are not single-stranded over their full length, but instead require a hairpin stem-loop. In fact, Bao teaches against using linear oligonucleotides. See, for example, column 30, line 56 through column 31, line 36 of Bao. Wittwer discloses one single-labeled polynucleotide with a fluorescent label attached to a terminal nucleotide. Wittwer does not disclose a second

polynucleotide labeled with a member of a FRET pair. To the contrary, to the extent that Wittwer discloses using a second polynucleotide, its label is such the second fluorescent emission signal is independent of the fluorescent emission signal of the first polynucleotide. See, for example, claim 35 at column 47, lines 19-35 of Wittwer. Wittwer also expressly teaches away from oligonucleotide pairs labeled with FRET pairs. See, for example, column 2, lines 1-19 of Wittwer. At most, the combined disclosures of Bao and Wittwer disclose a first single-labeled polynucleotide, and a second polynucleotide that must be a hairpin stem loop, wherein the first and second polynucleotides comprise labels that do not form a FRET pair. This is not the invention of claims 32 and 34".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since claim 18 does not require that the first single-stranded oligonucleotide and the second single-stranded oligonucleotide are complete single stranded oligonucleotides before hybridization and Bao *et al.,* teach that the first and second nucleic acid probes are single-stranded over their full length after they hybridize to the subject nucleic acid (see Figure 2), Bao *et al.,* do disclose that the first and second oligonucleotides are single-stranded over their full length as recited in claim 18. Second, although Wittwer *et al.,* do not teach a second polynucleotide labeled with a member of a FRET pair, the rejection is not dependent on Wittwer *et al.,* but is based on the combination of Bao *et al.,* and Wittwer *et al.*.

II In page 10, fourth paragraph bridging to page 11, fourth paragraph of applicant's remarks, applicant argues that "[A]pplicants respectfully assert that there exists no suggestion or motivation to combine Bao with Wittwer. To the contrary, the compositions disclosed by Bao absolutely require hairpin stem-loop oligonucleotides. Bao expressly teaches away from using

single-stranded or linear oligonucleotides at length by stating that the hairpin oligonucleotides have improved specificity and stability over linear oligonucleotides. See, column 30, line 56 through column 31, line 36 of Bao. In attempting to formulate an obviousness rejection by combining the disclosures of Bao and Wittwer by replacing a hairpin stem-loop oligonucleotide of Bao with the linear single-labeled polynucleotide of Wittwer, the Examiner is improperly changing the principle of operation of Bao, the primary reference. Furthermore, based on the disclosures of Bao, those of skill in the art would be dissuaded from using a linear rather than a hairpin stem-loop oligonucleotide. In view of Bao, those of skill in the art would certainly be disinclined from replacing one of the hairpin stem-loop oligonucleotides of the dual nucleotide FRET pairs described by Bao with a linear single-labeled polynucleotide that is not intended as part of a FRET pair described by Wittwer. Moreover, Wittwer teaches against using labeled polynucleotides with labels that comprise FRET pairs. See, column 2, lines 1-19 and claim 35 of Wittwer. Based on the disclosure of Wittwer, those of skill in the art would understand that the single-labeled polynucleotides described in Wittwer should not be used as a member of a FRET pair. Wittwer also appears to teach away from using dual oligonucleotides labeled with members of a FRET pair generally. Accordingly, the Examiner's proposed combination changes the principle mode of operation of Bao, the primary reference. Absent impermissible hindsight reconstruction, there exists no suggestion or motivation to combine the disclosures of Bao and Wittwer" and "[T]he Examiner's proposal of changing the principle mode of operation of Bao by introducing a linear single-labeled polynucleotide of Wittwer would leave the skilled person believing that there was no reasonable expectation of success by replacing a hairpin stem-loop

oligonucleotide with a label that is a member of a FRET pair with a linear single-labeled polynucleotide with a label that is not intended to be a member of a FRET pair".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since claim 18 does not require that the first single-stranded oligonucleotide and the second single-stranded oligonucleotide are complete single stranded oligonucleotides before hybridization and Bao *et al.*, teach that the first and second nucleic acid probes are single-stranded over their full length after they hybridize to the subject nucleic acid (see Figure 2), Bao *et al.*, do disclose that the first and second oligonucleotides are single-stranded over their full length as recited in claim 18. Second, there is a motivation for combining Bao *et al.*, and Wittwer *et al.*, together (see above rejection). Third, since the rejection is not dependent on "replacing one of the hairpin stem-loop oligonucleotides of the dual nucleotide FRET pairs described by Bao with a linear single-labeled polynucleotide that is not intended as part of a FRET pair described by Wittwer" as argued by applicant but is based on the simple substitution of one kind of fluorescent quencher (ie., Dabayl taught by Bao *et al.*,) from another kind of fluorescent quencher (ie., a nitroindole moiety taught by Wittwer *et al.*,) (see above rejection), the principle of operation of Bao *et al.*, is not changed. Fourth, although Wittwer *et al.*, do not teach a second polynucleotide labeled with a member of a FRET pair, the rejection is not dependent on Wittwer *et al.*, but is based on the combination of Bao *et al.*, and Wittwer *et al.*. Fifth, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of

ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

9. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bao *et al.*, in view of Wittwer *et al.*, as applied to claims 19, 20, 22, 32, 34, 38, and 43 above, and further in view of Nazarenko *et al.*, (US Patent No. 5,866,336, published on February 2, 1999).

The teachings of Bao *et al.*, and Wittwer *et al.*, have been summarized previously, *supra.*

Bao *et al.*, and Wittwer *et al.*, do not disclose further comprising at least one other component selected from a group consisting of a nucleic acid amplification primer, a template dependent nucleic acid polymerase, at least one deoxynucleoside triphosphate and a buffer for template dependent nucleic acid amplification reaction as recited in claim 39. However, Bao *et al.*, indicate that their nucleic acid probes are used in amplification reactions as primers (see column 15, first paragraph).

Nazarenko *et al.*, teach an upstream hairpin primer and a reverse primer (see Figure 2).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a solution recited in claim 39 by adding a nucleic acid amplification primer so that the nucleic acid amplification primer and one of nucleic acid probes taught by Bao *et al.*, form a primer pair in view of patents of Bao *et al.*, Wittwer *et al.*, and Nazarenko *et al.*. One having ordinary skill in the art has been motivated to do so because Bao *et al.*, indicate that their nucleic acid probes are used in amplification reactions as primers (see column 15, first paragraph). One having ordinary skill in the art at the time the

invention was made would have a reasonable expectation of success to add a nucleic acid amplification primer so that the nucleic acid amplification primer and one of nucleic acid probes taught by Bao *et al.,* form a primer pair.

10. Claim 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bao *et al.,* in view of Wittwer *et al.,* as applied to claims 19, 20, 22, 32, 34, and 43 above, and further in view of Segev (US Patent No. 5,437,977, published on August 1, 1995).

The teachings of Bao *et al.,* and Wittwer *et al.,* have been summarized previously, *supra.* In view of claims 32 and 42, since a plurality of FRET hybridization probes recited in claims 32 and 42 are identical, Bao *et al.,* in view of Wittwer *et al.,* teach a plurality of FRET hybridization probes recited in claim 42.

Bao *et al.,* and Wittwer *et al.,* do not disclose a solid support comprising a plurality of FRET hybridization probes as recited in claim 40.

Segev teaches that immobilizing the target nucleic acid molecule occurs before hybridizing the primary probe to the target nucleic acid molecule. The advantage of immobilizing the target nucleic acid molecule is that the unhybridized labeled molecules is separated from the immobilized complex prior to detection, thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a support comprising a plurality of FRET hybridization probes recited in claim 42 by immobilizing the subject nucleic acid taught by Bao *et al.,* to a support before hybridization in order to form a support comprising the plurality of

FRET hybridization probes and the subject nucleic acid in view of patents of Bao *et al.*, and Wittwer *et al.*, and Segev. One having ordinary skill in the art has been motivated to do so because Segev suggests that immobilizing the target nucleic acid molecule before hybridization assay would enhance separation of unhybridized molecules from the immobilized complex prior to detection and thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to make a support comprising a plurality of FRET hybridization probes as recited in claim 42.

Response to Arguments

In page 12, first and second paragraphs of applicant's remarks, applicant argues that "Segev does not cure the deficiencies of Bao and Wittwer and there is further no motivation or suggestion to combine Segev with Bao and Wittwer".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, since claim 18 does not require that the first single-stranded oligonucleotide and the second single-stranded oligonucleotide are complete single stranded oligonucleotides before hybridization and Bao *et al.*, teach that the first and second nucleic acid probes are single-stranded over their full length after they hybridize to the subject nucleic acid (see Figure 2), Bao *et al.*, do disclose that the first and second oligonucleotides are single-stranded over their full length as recited in claim 18. Second, there is a motivation to combine Bao *et al.*, and Wittwer *et al.*, and Segev (see above rejection).

11. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bao *et al.*, as applied to claims 19, 20, 22, and 43 above, and further in view of Segev.

The teachings of Bao *et al.*, have been summarized previously, *supra.* In view of claims 18 and 40, since a plurality of FRET hybridization probes recited in claims 18 and 40 are identical, Bao *et al.*, teach a plurality of FRET hybridization probes recited in claim 40.

Bao *et al.*, do not disclose a solid support comprising a plurality of FRET hybridization probes as recited in claim 40.

Segev teaches that immobilizing the target nucleic acid molecule occurs before hybridizing the primary probe to the target nucleic acid molecule. The advantage of immobilizing the target nucleic acid molecule is that the unhybridized labeled molecules is separated from the immobilized complex prior to detection, thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a support comprising a plurality of FRET hybridization probes recited in claim 40 by immobilizing the subject nucleic acid taught by Bao *et al.*, to a support before hybridization in order to form a support comprising the plurality of FRET hybridization probes and the subject nucleic acid in view of patents of Bao *et al.*, and Segev. One having ordinary skill in the art has been motivated to do so because Segev suggests that immobilizing the target nucleic acid molecule before hybridization assay would enhance separation of unhybridized molecules from the immobilized complex prior to detection and thereby reducing the background and increasing the signal-noise ratio (see column 17, lines 3-14). One having ordinary skill in the art at the time the invention was made would have a

reasonable expectation of success to make a support comprising a plurality of FRET hybridization probes as recited in claim 40.

Response to Arguments

In page 12, fourth paragraph of applicant's remarks, applicant argues that "Segev does not cure the deficiencies of Bao and there is further no motivation or suggestion to combine Segev with Bao for the reasons discussed above".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, since claim 18 does not require that the first single-stranded oligonucleotide, and the second single-stranded oligonucleotide are complete single stranded oligonucleotides before hybridization and Bao *et al.,* teach that the first and second nucleic acid probes are single-stranded over their full length after they hybridize to the subject nucleic acid (see Figure 2), Bao *et al.,* do disclose that the first and second oligonucleotides are single-stranded over their full length as recited in claim 18. Second, there is a motivation to combine Bao *et al.,* and Segev (see above rejection).

Conclusion

12. Claims 35, 37, and 44 are allowed over prior art.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

March 2, 2007

FRANK LU
PRIMARY EXAMINER